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A SIMPLE, UNEXPECTED REGIOSELECTIVE CHLORINATION OF A SERIES OF 5-OH-2-(ALKYLAMINO)TETRALINS: POTENTIAL DOPAMINERGIC AGENTS

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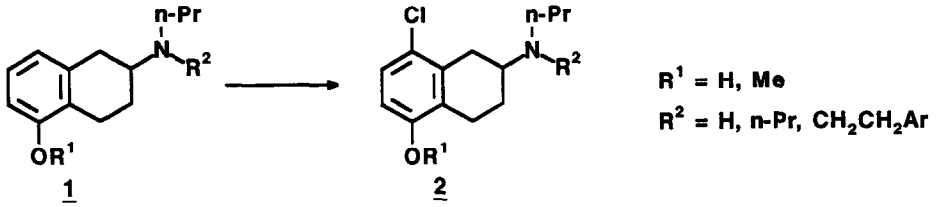
Abstract: A series of 8-chloro-5-hydroxy-2-(alkylamino)tetralins were prepared in a one-step reaction using a hexachlorocyclohexadienone as regioselective chlorinating agent. The reaction proceeds in a highly selective but unexpected manner.

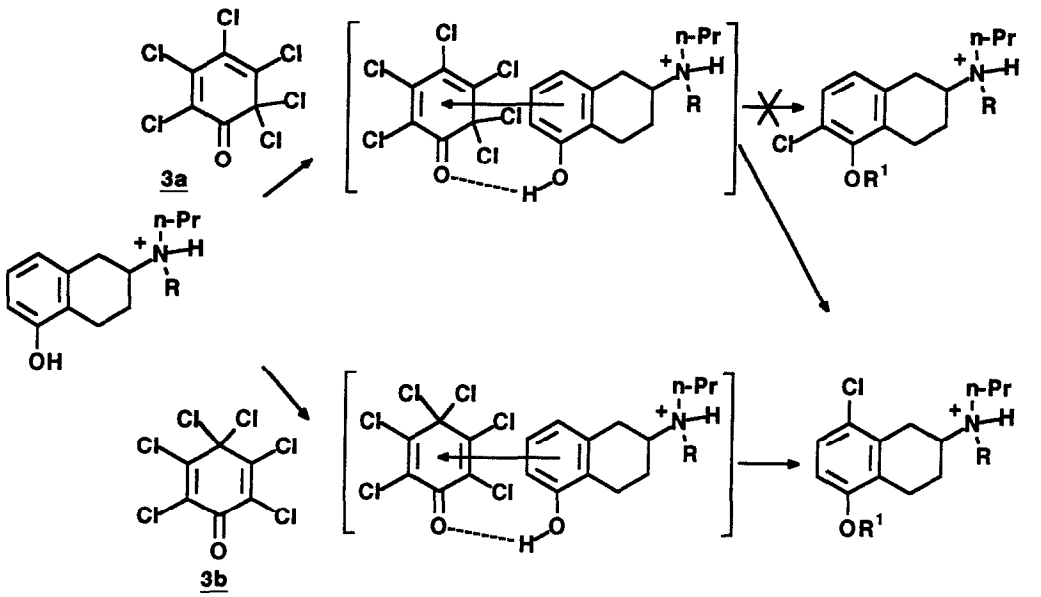
A number of monophenolic 2-aminotetralins (1) are potent and selective dopamine receptor agonists with potential therapeutic utility in a number of diseases, such as e.g. Parkinson's disease.[1] As part of our current efforts to elucidate the structure activity relationship of dopaminergic agents we have synthesized the 8-chloro derivatives 2 (Scheme I). Compared to the hydroxylated 2-aminotetralins 1, chlorination will cause a different electronic density at the aromatic ring and therefore a different pK_a of the phenol. Such a property might contribute to the pharmacological profile of these compounds, when tested *in vivo* and *in vitro* for their



Scheme I

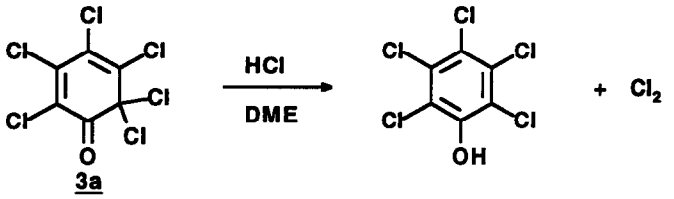
affinity at different receptors.[2] In reported syntheses of chlorinated aminotetralin derivatives the compounds are usually constructed starting with a commercially available polysubstituted benzene derivative[3]. The presence of the corresponding non-chlorinated aminotetralins on the shelf made such a lengthy synthesis unattractive and prompted us to investigate the feasibility of a single step reaction for the regioselective production of the desired compounds. Guy et al.[4] have shown that remarkable selectivity can be obtained by using specific chlorinating agents such as hexachloro-2,4-cyclohexadienones (3a,b). The regioselectivity is attained by using a reagent tailored in such a way that it is capable to participate in donor acceptor and H-

bonding interactions. Since the aromatization energy of the cyclohexadienones acts as the driving force, reactions can be performed under extremely mild conditions. We have therefore applied this approach to the synthesis of chloro-aminotetralins. It seemed reasonable to expect that by use of the two tailor-made hexachlorocyclohexadienones, **3a** and **3b**, the aminotetralins would be chlorinated at the 6- and 8-positions, respectively (Scheme II). We did indeed find that the combination of 1.2 equivalents of 2,3,4,5,6,6-hexachloro-2,4-cyclohexadiene-1-one **3a** (the ortho chlorinating agent) and the sparingly soluble hydrochloride salts of the aminotetralins **1** in DME at room temperature did monochlorinate the substrates within 3 h in good yield. However, under the reaction conditions used, the 8-chloro isomers, and not the expected 6-chloro-5-hydroxy-2-(dialkylamino)tetralin hydrochlorides precipitated completely from solution upon addition of diethylether. The regioselectivity was established by comparing the ^{1}H and ^{13}C NMR spectra of the chlorinated products with those of products obtained via an unambiguous route. Using 6- or 7-hydroxy isomers as substrates in which only ortho positions are available, the reaction leads to poor yields, even after 24 h. These findings indicate that the reactions do not proceed according to the proposed mechanism[4]. A possible explanation might be that the hexachlorocyclohexadiene slowly reacts with the hydrochloric acid to give a very low concentration of chlorine (Scheme III). The main evidence in support of this mechanism is as follows: (a) Pentachlorophenol was formed in a dry HCl-DME solution of **3a**. (b) A 12 : 1 mixture of monobrominated and monochlorinated products was obtained when the hydrobromide salt was used in stead of the hydrochloride salt. In that case,

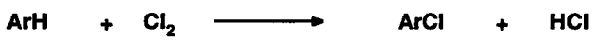


Scheme II

the halogenating species is probably the interhalogen compound (Br-Cl). (c) Very poor yields were obtained when the free amines were halogenated under the same conditions, when chlorine is less easily formed. (d) The reaction of a mixture of 50% of the free amine and 50% of the hydrochloride salt gave a yield of about 50%. With the less activated 5-methoxy derivatives only 50% yield is obtained after 24 h. This reaction is strongly catalyzed by the Lewis acid $AlCl_3$, probably by polarizing the chlorine.



3a



Scheme III

Since chlorine is a very reactive and small chlorinating agent it would be expected to give the lowest para/ortho ratio and considerable dichlorination even when less than 1 equivalent of chlorine is formed, but only para-chlorinated products were obtained. GC/MS analysis have proved that the total yield of other isomers (ortho chloro- and dichloro-compounds) did not exceed 1.1%. Apparently, the very low concentration of the formed chlorine is, as in reactions of NBS and NCS, a reason for the found selectivity. In addition, hydrogen bonding could play a major role in obtaining the observed high regio selectivity. Formation of hydrogen bonds between the phenolic proton and the solvent DME sterically hinders the ortho approach of the electrophile.[5] Another mechanism for the chlorination of the phenol is feasible according to the same scheme as proposed by Lindsay Smith and coworkers[6]. In the first step of the reaction, **1** and **3a** undergo halogen exchange to produce the N-chlorinated aminotetralins. These authors have shown that a remarkable para selectivity can be obtained by using N-chloroamines. However, according to this mechanism the route to the brominated products would become very complicated.

In summary, the observed regioselectivity may be rationalized by a very low steady-state concentration of chlorine, formed from the reaction of hexachloro-2,4-cyclohexadienone with the hydrochloride salts of the aminotetralins, and steric effects due to the formation of hydrogen bonds between the solvent and the phenolic proton. These preliminary results show that the method is very suitable for the para-chlorination of hydroxylated aminotetralins and related compounds, because of the ease of handling, acceptable reaction rate, and nondestructivity towards the phenol and amine functions and should be a valuable reaction in the repertoire of synthetic medicinal chemists. For the less reactive methoxy derivatives Lewis acid catalysis may

be however necessary. We are currently investigating the scope and limitations of this reaction.

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7. Typical Procedure: Under a nitrogen atmosphere, in a three-neck round-bottom flask were placed 5 mmol of 5-hydroxy-2-(dipropylamino)tetralin.HCl (**1**.HCl, R^2=n-Pr) and 300 mL of dry DME. To this stirred suspension was added 7 mmol of 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one (**3a**). The progress of the reaction was monitored by tlc and was complete in 2 to 3 h. The mixture was diluted with 200 mL ether and the solid was collected by filtration. The resulting hydrochloride salt was recrystallized from MeCN-Et_2O to give 86% of 8-Chloro-5-hydroxy-2-(dipropylamino)tetralin: mp 204-205 °C; MS (CI with NH_3) m/e 282 (M+1), 284 (M+3); ^{13}C-NMR (300 MHz, D_2O) 153.80, 131.83, 126.70, 124.62, 122.49, 113.48, 58.91, 51.80, 51.46, 27.57, 22.99, 21.78, 17.89, 11.15; ^{1}H-NMR (300 MHz) 7.19 (d, 1H, J = 1.92 Hz), 6.83 (d, 1H, J = 1.92 Hz); Anal. ($C_{16}H_{24}NClO.HCl$), C, H, N, Cl.